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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Stuart L. Schreiber

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TWO INTERNATIONAL PLACE
BOSTON, MA 02110

EXAMINER

VOGEL, NANCY TREPTOW

ART UNIT

PAPER NUMBER

1636

NOTIFICATION DATE

DELIVERY MODE

05/29/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No. 09/834,424	Applicant(s) SCHREIBER ET AL.	
	Examiner NANCY VOGEL	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/2/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/09 has been entered.

Claims 8-29 are pending. Receipt of the Information Disclosure Statement of 3/2/09 is acknowledged.

Information Disclosure Statement

References which are crossed through on the Information Disclosure Statement have not been considered since they are in the French language and no explanation of their relevance or content has been submitted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method of making an agent that effects cells in a biological event mediated by the association of two or more endogenous cell surface receptor molecules, wherein said agent includes a first and second non-peptidic moiety that bind to cell surface receptor molecules, wherein said agent binds to both cell surface receptor molecules. The claims read on preparing a broad genus of agents to be used in the claimed method of effecting cells in a biological event.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims the agent by function only, whereby the agent causes the oligomerization of two or more protein mediators in a manner which effects a

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biological event mediated by association of two or more endogenous cell surface receptor, without any disclosed or known correlation between the structure of the agent and the protein mediators with which it interacts to effect a biological effect. The specification only provides teachings regarding the structures of agents that bind to immunophilin receptors, but does not teach which of these agents necessarily results in effecting a given biological event, more specifically the activation of a signal transduction cascade. Furthermore, even if it were demonstrated that the immunophilin-oligomerizers were capable of activating a signal transduction cascade, these teachings do not provide a written description of what agents would have a similar function on the hundreds of additional cell surface receptors/proteins involved in various other signal transduction cascades. This is because the structures responsible for causing the oligomerization (and subsequent activation of immunophilin-based signaling cascades) will not bind to and activate other cell surface receptors and their respective signaling cascades. The simple fact is that the skilled artisan could not envision how to activate hypothetical Signal Cascade "X" based on the instant specification because there is no description of what genus of agents will oligomerize hypothetical Receptor "X." Based on the teachings of the specification, the skilled artisan cannot envision the broad genus of agents to be made in the claimed method because the skilled artisan cannot envision which agents will bind to and effect a biological event for any given protein mediators (e.g., cell surface receptors).

The art at the time of filing of the instant specification does not provide sufficient information on the subject to overcome the deficiencies of the instant specification as it

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regards envisioning the broad genus of agents to be used in the claimed invention.

There is no description in the prior art that allows one to envision a representative number of agents having the ability to induce a signal transduction cascade in a cell by disclosing structural or functional features of such agents so that one of skill in the art could envision the claimed invention. Indeed, it is noted that in publications subsequent to the filing date of the instant specification, there is an identification of agents for specific receptors that are not described or even remotely considered in the instant application (see for example Qureshi et al. (Proc. Natl. Acad. Sc. USA, 96:12156-12161, 1999) and Tian et al. (Science , 281: 257-259, 1998), IDS references cited 10/1/02); henceforth Qureshi and Tian). Qureshi identified compounds 1 and 5, novel compounds synthesized in that study (see for instance Materials and Methods and Figure 1,, pages 12156-12157,

bridging paragraph) that had the capacity to oligomerize the EPO receptor (see for example the Abstract). Tian identified compound SB 247464 (see for example Figure 1) that had the capacity to oligomerize the G-CSF receptor and activate a signal transduction cascade (see for example the Abstract). Nowhere in either the instant specification or the art at the time of filing is there a description that these particular agents had the capacity to oligomerize those (or any) particular receptors, or even a description that agents having structures similar to those agents had such a capacity. Thus, the skilled artisan cannot rely on the prior art to envision a sufficient number of agents to be used in the instant invention.

Furthermore, the European opposition proceedings documents present in the IDS filed 3/2/09, point to additional evidence to support the rejection. They point to the reference to Connolly et al. (Bioorganic and Medicinal Chemistry Letters 10 (2000) 1995-1999) (cited in Information Disclosure Statement of 3/2/09). Connolly et al. teaches, e.g. at the two concluding paragraphs (at pages 1997 and 1998) that the compounds ("dimers" in their parlance) tested had high affinity for the EPO receptors, but failed to show EPO-mimetic activity as expected. As such, it is apparent that the relationship of structure of a small, non-peptidic molecule to its function in dimerization, even where affinity is high for one subunit of the receptor at a time, was not well enough understood at the time of filing to have permitted one of skill in the art to have recognized that Applicants were in possession of the full scope of the claims. No successful examples to contradict this conclusion were present in the instant specification.

Neither the instant specification nor the art at the time of filing describes a structure-function relationship for a representative number of agents as it relates to the receptors upon which they can act. As a result, the skilled artisan would not be able to envision the broad genus of agents to be used in the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

The following is a new rejection :

Claims 8-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (United States v. Teletronics., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Exparte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The invention is a method of preparing an oligomerizing agent to affect a biological event; in specific embodiments, the biological event is the activation of a signal transduction cascade. In order to practice the claimed invention, the skilled artisan would need to understand which agents were capable of oligomerizing a given set of protein mediators in a fashion that would activate a signal transduction cascade. It is noted that such agents would need to be known in order to practice the invention, and that the ability to identify these agents does not provide the requisite ability "to use" the claimed invention, set forth in the enablement requirement.

Breadth of the claims. The claims are very broad, claiming the ability to use any agent

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to affect a biological event, without a description of a structure-function relationship between a given agent and its cognate protein mediator.

State of the art. At the time of filing, the art was insufficient to describe the broad genus of agents set forth in the claims as having the functional capacity to oligomerize a given set of protein mediators in a manner that activated a signal transduction cascade.

Although the state of the art does describe agents capable of oligomerizing chimeric receptor proteins, it is noted that these chimeric receptors are specifically designed to bind to these agents, and do not represent the wide array of endogenous receptors the claimed method intends to oligomerize and activate signal transduction through. Without teachings in the art prior to the filing of the instant specification as to which agents could be used to oligomerizing certain endogenous protein mediators in a manner that affects a biological event, the skilled artisan would be required to consult the instant specification as to which agents could be used.

It is additionally noted that, in post-filing art (Qureshi and Tian, as recited above), novel agents that were not described in the instant specification were identified as having the capacity to oligomerize and activate a signal transduction cascade. Neither of these agents are taught by the instant specification, nor is there a teaching that agents having a similar structure would activate a signal transduction cascade via any protein mediator.

Number of working examples and Guidance provided by applicant. The instant specification provides little support or guidance directing the skilled artisan as to which agents can be used to affect a biological event, and through which protein mediators

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such agents would work. The instant specification does describe small, non-peptidic compounds that are capable of oligomerizing immunophilin receptors, although it is unclear that these agents are sufficient to affect a biological response. Furthermore, even if these agents were presumed to induce an immunophilin-based biological event, these agents are not representative of the broad genus of agents that are claimed for use in the instant invention. Specifically, those immunophilin-oligomerizing agents would not have the capacity to oligomerize non-immunophilin receptors because the structures of the agents would not be sufficient to bind to other receptors, let alone oligomerize them. Without a description of which agents can be used to oligomerize a given protein

mediator, and which signal transduction cascade this event would activate, the skilled

artisan could not use the claimed invention across the broad scope in which it is claimed.

Unpredictability of the art and Amount of experimentation required. The invention is highly unpredictable in view of the nature of the invention, the broad scope of the claims and the teachings instant specification in view of the state of the art. In order to practice the claimed invention, the skilled artisan would need to know what agents could oligomerize a given protein mediator associated with a particular signal transduction cascade, and then apply that agent to a cell of interest. However, neither the instant specification nor the state of the art at the time of filing describes a representative number

(and in most cases, even a single example) of such agents for even one endogenous

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receptor, let alone any receptor or combinations thereof that are involved in a given signal transduction pathway. As a result, the ordinary skilled artisan would be required to empirically identify a vast number of agents for each receptor and heterologous combinations thereof, and determine which agents corresponded to which receptor combinations for activation of the respective signaling cascade (i.e., the skilled artisan is required to perform an inventive step in order to use the claimed invention). This is evidenced by the post-filing art, wherein two groups (Qureshi and Tian) had to identify compounds de novo, in order to oligomerize a particular receptor to induce a signaling cascade. Importantly, the compounds identified in Qureshi and Tian are not described in the instant specification or the art at the time of filing, either specifically or in terms of a generalized structure having the capacity to oligomerize any particular receptor. This demonstrates that undue and unpredictable trial and error experimentation would be required to practice the claimed invention, because agents that were not even identified in the instant specification or the art at the time of filing are needed to practice the claimed invention. If the agents to practice the invention must still be identified, then it is impossible for the skilled artisan to use an invention that requires the identity of the agent. Because the skilled artisan would be required to identify agents in order to use the claimed invention, the claimed method is not enabled. Furthermore, as evidence that the post-filing date art showed great unpredictability in the ability to prepare an agent including a first and second non-peptidic moiety that each bind to one of the cell surface receptor molecules, and which effects a biological event mediated by the

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association of the cell surface receptor molecules, Connolly et al. teaches, e.g. at the two concluding paragraphs (at pages 1997 and 1998) that the compounds ("dimers" in their parlance) tested had high affinity for the EPO receptors, but failed to show EPO-mimetic activity as expected. The mere ability to design a small molecule which can bind to receptor subunits does not lead predictably to the intended or desired physiological effect. As such, each embodiment produced would have to be tested empirically, with limited hope of success, in view of Connolly et al. Such would have been deemed undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NANCY VOGEL whose telephone number is (571)272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/NANCY VOGEL/
Primary Examiner, Art Unit 1636

NV
5/22/09